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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,839	01/07/2005	Robert J. Mathvink	21139YP	2759

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MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/520,839	MATHVINK ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-20* is/are allowed.

6)☒ Claim(s) *21-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/4/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-39 are pending.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 4/04/2006, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating and controlling diabetes, does not reasonably provide enablement for ameliorating or reducing the risk of diabetes as well as treating, controlling, ameliorating or reducing the risk of various disease and disorders based inhibition of Dipeptidyl Peptidase IV (DP-IV) as embraced in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence

or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention:

The instant claims 21- 28 are drawn to a method of treating and or controlling diabetes, for ameliorating or reducing the risk of diabetes as well as treating, controlling, ameliorating or reducing the risk of various disease and disorders while claims 29-39 include additional therapeutic agents along with the compound of claim 1 for treating and or controlling diabetes, for ameliorating or reducing the risk of diabetes as well as treating, controlling, ameliorating or reducing the risk of various disease and disorders.

Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the DP-IV inhibiting activity by the instant compounds, instant claims reaches through inhibiting and treating any or all diseases and disorders in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of DP-IV, based on limited assay, it is claimed that treating any or all diseases in general, which there is no enabling disclosure.

According to specification and instant claims 21-28, such method diseases or disorders includes treating, controlling, ameliorating or reducing the risk of

hyperglycemia, treating, controlling, ameliorating or reducing the risk of obesity treating, controlling, ameliorating or reducing the risk of insulin resistance, treating, controlling, ameliorating or reducing the risk of one or more lipid disorders selected from the group consisting of dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low I-]DL, and high LDL treating, controlling or preventing atherosclerosis along with a list of diseases: (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low I-IDL levels, (11)high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), (25) Type 2 diabetes, (26) growth hormone deficiency, (27) neutropenia, (28) neuronal disorders, (29) tumor metastasis, (30) benign prostatic hypertrophy, (32) gingivitis,(33)hypertension, (34) osteoporosis, and other conditions that may be affected by inhibition of DP-IV, for which there is no enabling disclosure.

Inflammation is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly,

treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Moreover many if not most of central nervous system diseases such as Alzheimer's disease, ALS, multiple sclerosis etc. are very difficult to treat. For multiple sclerosis alone there is no known drug, which can successfully reverse the course of the disease, despite the fact that there are many drugs, which act on nicotinic receptor.

The scope of the claims includes treatment of various diseases, which is not adequately enabled solely based on the activity of the compounds provided in the specification. The instant compounds are disclosed to have DP-IV inhibiting activity and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as DP-IV inhibitor that would be useful for treating and preventing all diseases stated above. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover, many if not most of diseases such as type I diabetes, various cardiovascular diseases are very difficult to treat and despite the fact that there are many drugs, which can be used for treating type II diabetes and hypertension.

The scope of the claims involves thousands of compounds of claim 1, as well as the thousand of diseases embraced by the list shown above.

Specification in page 16 provides for an assay for DP-IV inhibition and based on these studies it is recited that the instant compounds would useful to treat and prevent all diseases. In addition, while prior at provides support for treating type II diabetes, which is non-insulin dependent, based DP-IV inhibition, there appears to be no support for type I diabetes, which is insulin dependent, Instant claim 21 generically includes both types of diabetes. Specification has not provided any evidence or nexus that because of the mode of action of the instant compound, the compound would be useful for treating both types of diabetes.

There are several disease/disorders and that one class of compound can be used to treat all of them is an incredible finding for which applicants have not provided adequate support in the specification. A reasonable correlation is necessary to demonstrate such utilities. See Ex parte Stevens, 16 USPQ 2d 1379 (BPAI 1990); Ex parte Busse et al., 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study").

In addition, the scope of the claims includes ameliorating or reducing the risk of the said disease, which amount to preventing these diseases. The term "to prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Webster's II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed

herein.

No compound has ever been found to treat and or prevent any or all diseases and disorders of all types stated above. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of modern medicine. Each specific disease or disorder has unique biologic and clinical features that must be appreciated for proper diagnosis and treatment. Different diseases affect different organs and have different symptoms. Thus, it is beyond the skill of modern medicine today to get an agent to be effective against all diseases and disorders generally despite the fact that they may common mode of action.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the PPAR binding activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. The state of the art is indicative of the requirement for undue experimentation. See Green et al., Expert Opin. Emerging Drugs, 11(3); 525-539, 2006.

2) The state of the prior art:

There are no known compounds of similar structure, which have been demonstrated shown to be useful for both types of diabetes and treating and preventing all diseases. For example, the notion that a compound could be effective against all or any diseases because of its in interaction with a single target, in the instant case DP-IV, in general is absolutely contrary to our current understanding of pharmacological basis of drug design and treatment of diseases. In fact, a specific target is often chosen to treat a specific disease or that specific target related diseases. Indeed, applicants' instant claims 29-39 rely on this fact for treating disorders recited therein with additional therapeutic agents. If the compounds were to that effective that it can be used to treat all diseases as stated above and also prevent them, there would be a need for additional agents. Furthermore, the prior art search in the related area does not suggest that because of the mode of action of a compound, as DP-IV inhibitor, it would be useful for all disorders generically embraced in the claim language. See Green et al.,

3) The predictability or lack thereof in the art:

As noted above, although there several prior art which teach similar compounds as DP-IV inhibitor, they do not teach use of the compound disclosed for treating and preventing any or all disorders, besides type II diabetes and hence there is no art predictability or assurance that instant compound would do so. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely

with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present:

Specification provides no guidance or direction as to how would one use the instant compound to treat all or any disorder besides type II diabetes.

5) The presence or absence of working examples:

There are working examples to show that how the instant compound could be used to treat all disorders wherein DP-IV is implicated as causative agent.

6.The breadth of the claim:

The breadth of the claim, with given large genus outlined above, is broad enough to include treating any or all diseases including those yet to be discovered for which there is no pharmacological basis or showing in the specification.

7) The quantity of experimentation needed:

The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in

the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Allowable Subject Matter

Claim 1-20, barring finding of any prior art in a subsequent search, would be allowed. Said claims would be allowed as prior art search in the related area did not teach or suggest the compound and composition embraced in these claims. In addition, an obviousness-type double patenting is precluded in view of proviso in the claims of the copending application 10/542,694.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any

inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

Venkataraman Balasubramanian

10/29/2006